Journal of Current Biomedical Reports
Volume 3, Number 1, 2022
jcbior.com
eISSN: 2717-1906

Review

Brain neural network, development, microbiome, microbial toxins and COVID-19

Ali Samrezaee[1], Maryam Doustmehraban[2], Naimeh Ghadimi[3], Sedigheh Bahador[4], Arash Barghi[5], Erfan Ghanbarzadeh[6], Amir Rigi[7], Mojtaba Hedayati Ch[8,*], Atiyeh Kimiaeifar[9]

[1]*School of Basic Medical Sciences, Academy of Medical Science, Zhengzhou University, Zhengzhou, China*
[2]*Student Research Committee, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran*
[3]*Student Research Committee, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran*
[4]*Student Research Committee, School of Medicine, Esfahan University of Medical Sciences, Esfahan, Iran*
[5]*Student Research Committee, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran*
[6]*Student Research Committee, School of Medicine, Guilan University of Medical Science, Rasht, Guilan, Iran*
[7]*Microbial Toxins Physiology Group, Universal Scientific Education and Research Network, Rasht, Iran*
[8]*Department of Microbiology, Virology and Microbial Toxins, School of Medicine, Guilan University of Medical Sciences, Rasht, , Iran*
[9]*Iran University of Medical Sciences, Tehran, Iran*

Abstract

Although almost 2 years have passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in the world, there is still a threat to the health of people at risk and patients. Specialists in various sciences conduct various researches in order to eliminate or reduce the problems caused by this disease. Neural network science plays a vital role in this regard. It is important to note the key points of neuro-microbial involvement in the diagnosis and management of COVID-19 therapy by physicians and patients whose nervous systems are challenged. The relationship between COVID-19, microbiome and the profile of microbial toxins in the body is one of the factors that can directly or indirectly play a key role in the body's resistance to Covid-19 and changes in the neural network of the brain. In this article, we introduce the relationship and behavioral and mood problems that can result from neuronal changes. In linking the components of this network, artificial intelligence (AI), machine learning (ML) and data mining (DM) can be important strategies to assist health providers to choose best decision based on patient's history.

Keywords: COVID-19, Brain, Neural network, Microbial toxins, Machine learning

1. Introduction

Coronavirus disease 2019 (COVID-19), known as significant public health challenge worldwide and is the causative agent of severe acute coronavirus respiratory syndrome. Since December 2019, the COVID-19 outbreak has become a significant universal pandemic threat for almost all people and specially patients with specific disabilities [1, 2]. In pandemic situation, we are in constant struggle to stop virus infection or attenuate severity of disease every day [3]. Scientists in different fields tend to do their best, monitoring and managing disease. Because of complicated nature of neural network abnormalities and coinfections, it seems that there is a need for multidisciplinary research and performance based on complex systems biology of human neural

[*]**Corresponding author:**
Mojtaba Hedayati Ch, Ph.D
Department of Microbiology, School of Medicine,
Guilan University of Medical Sciences, Rasht, Iran
Tel/Fax: +98 13 33326061/+98 13 33326061
Email: mhedayatich@gums.ac.ir
https://orcid.org/0000-0002-8277-9841

Received: October, 10, 2021
Accepted: January, 12, 2021

network-microbiome interaction in patient suffered from COVID-19 [4].

We are focouseing on human neural network, microbial toxins profile, and computer science-based research as a comprehensive monitoring strategy package against COVID-19. For this purpose, it is necessary to explain a series of concepts to understand the network relationship between these sciences, which we will describe as follows.

2. Brain neural network development, microbiome, microbial toxins and COVID-19

Since the clinical symptoms of COVID-19 focus more on respiratory symptoms, its consequences on the central nervous system (CNS), brain neural network development (BNN) have received less attention. However, in some cases, respiratory failure may occur following infection of the brainstem and affecting the respiratory centers [5]. The exact mechanism and relationship of neurological consequences in patients with coronavirus is not known. Some receptors for the virus, such as angiotensin-converting enzyme 2 (ACE2), appear to be less abundant in the brain, causing peripheral nerves to become infected more rapidly than CNS [4]. Neural pathways and neural networks are gateways for viruses to enter CNS. Viruses can internalize to cell via antrograde or retrograde neurotransmitters movement by infecting the base of sensory or motor nerve terminals [5].The olfactory nerve terminals which are coming from the frontal sinus are considered high-risk routes virus gate to CNS [6]. This route is converted to a conduit between the nasal epithelium and the CNS due to the unique structure of the olfactory nerves and olfactory bulb in the nasal cavity and frontal lobe of the brain. Coronaviruses can thus reach the brain through the nose and the olfactory cavity. Within 7 days, viruses that infect nasal cells can reach the brain and cerebrospinal fluid (CSF) via the olfactory nerve and produce demyelination owing to inflammation and response [7]. The detection of high levels of the virus in the brainstem after the onset of coronavirus also indicates the transmission of the virus to the CNS through the respiratory tract, which is associated with neurodegenerative diseases. Involvement of this area of the brain indicates the role of respiratory and cardiac control centers in COVID-19-induced acute respiratory syndrome [8].

The growth and development of the neural network (NN) is one of the most known important requirements for human physiological stability [9]. This evolution could depend on different variables like genetic, microbiome, total microbial toxins profile, bodies regulatory systems and so on. Maturation of human NN might affected during microbiome dysbiosis that itself, caused mood changes and sickness behaviours [9, 10]. Even it shows that difference in gut-brain axis between individuals and its microbiota composition diversity could lead to changes in human personality traits. The composition and diversity variations in the gut microbiota are linked to personality differences, including sociability and neurological disorders [11, 12].

It has been shown that social interactions can increase the diversity of the gut microbiome and the NN, and people with higher stress or anxiety have lower microbiome diversity. This discussion is very important in relation to some neurological diseases such as autism and can be examined in relation to other neurological diseases as well [11]. Nutrition can also play an important role in regulating NN growth by affecting the microbiome. For example, studies have shown that adults who were not breastfed as children had fewer microbiomes as adults [13]. Studies showed that, proper formation and ratio of the microbial population in life is indispensable for approporiate NN development [14].

In addition to the microbiome, microbial secondary metabolites, such as microbial toxins, can affect the physiology and behavior of the neural network [15]. Occupational exposure, daily routine, food consumption cultures and environmental factors in many places of the world are effective in the formation of different human microbiota and total microbial toxins volume in different forms. It is very important to monitor the relationship between NN development, microbiome and their toxins (such as lipopolysaccharide; LPS) especially in COVID-19 patients. Because direct or indirect effects of microbiota and microbial toxins volume on BNN development is unavoidable [16-18]. Previous studies have shown that LPS (as a systemic inflammatory toxin), could lead to synaptic loss and cognitive decline in both animal models and human [5]. Part of this is due to the effect of LPS on stimulating the secretion of inflammatory cytokines, and part is related to the activation of microglia and the population of blood

cells such as platelets [5, 19]. Nowadays in some studies, developing brain is considering as an innate immunity key regulator and central player in brain-developmental origin immune cells interaction of the body [20]. Therefore, it makes sense to consider acute, chronic, and even fetal stimuli by immune stimulants (such as microbial toxins) as an interfering factor in this sensitive pathway. Based on "leaky gut-brain hypothesis", many microbial toxins will affect the growth and development of the neural network and the brain through this mechanism [21, 22]. Many studies have been done so far that show that in various neurological diseases, this microbial-microbial toxin association can be used for therapeutic purposes in many diseases. A therapeutic applications of some bacterial protein like: *Clostridium botulinum* Botulinum neurotoxin (BoNT), *Bacillus anthracis* Lethal toxin (LF), *Bordetella pertussis* Pertussis toxin (PTX), *Escherichia coli* Cytotoxic nectorizing factor1 (CNF1) and Chlorotoxins have previusely presented as an immunotoxins or other form to attenuate a series of disease [12, 23]. Another members of bacterial toxins like neurotoxins are multipotential toxins which could consider as interacting agents with NN and neuronal cells. They can target different NN include: motoneurons, inhibitory interneurons, hippocampal neurons, enterocyte neurons, Enterochromaffin cells and vagal nerve, enterochromaffin cells and enteric neurons [24, 25].

During infection with COVID-19, the microbiome, microbial populations, and the volume and type of microbial toxins in the body can change. These changes or accidental coinfection of individuals can have different effects on the growth and function of the brain's neural network [26]. These effects are very diverse and can range from stimulation of the vomiting center in the brain to stimulation of glutamate (Glu)-acetyl cholin (Ach)-gama amino butyric acid (GABA)-glycin (Gly) release and apoptosis of brain neurons. A series of neurotransmitters and neuropeptides realease or blocking also could affect during exposure with some bacterial neurotoxins. The most important neurotransmitters in this case include: Ach, Glu, Aspartate (Asp), GABA, Gly, Dopamine (Dopn), Adrenalin (Adrln), Noradrenalin (NAdrln), Seretonin (or 5-HT), Adenosine triphosphate (ATP) corelease with Ach and Nicotinamide adenine dinucleotide (NAD), Calcitonin gene-related peptide (CGRP), Vaso intestinal peptide (VIP), Neuropeptide Y, SP and Nitric oxide (NO) [24].

One of the problems in studying the biology of systems related to microbiome-microbial toxins and their effects on neural networks is the existence of many variables. If there is a way to classify or categorize these variables and find their relationships, the possibility of predicting, preventing, and treating management is not unexpected.

3. Machine learning as a promising strategy

Different methods have been used till now to increase the effectiveness of COVID-19 prophylaxis or treatment include personal hygiene prevention, nutrition, lifestyle changes and vaccinations [27]. However, no interdisciplinary viewpoint has been established to assess the acquired data. We suggest artificial intelligence (AI), machine learning (ML), and data mining (DM) as multipotentially relevant ways for integrating the components of the microbiome, microbial toxins, NN, and COVID-19 network.

In brief, AI utilized automated ways of computing, reasoning and inference by computers. ML is a subset of AI. It converts data into information and makes decisions based on this conversion. Most indispensable algorithms in this case are: classification, clustering, feature selection and prediction. On the other hand, DM do extracting information from a massive data. DM is not a technical discipline but uses different algorithms related to natural language processing (NLP), ML and AI. It is capable to search within different programs, manuscript abstracts and create question-answer systems to classify data and make conclusion [28]. These computer sciences help computers to behave intelligently and perform various tasks.

ML has the capacity to generalize data from expansive sums of information and can utilize calculations to recognize connections and d esigns between comes about of DM, get valuable comes about, and take modern activities [29]. DM, AI, and ML are three sciences that, in expansion to their contrasts, are moreover straightforwardly related to each other [30].

Modern medicine produces a lot of data obtained from COVID-19 cases. ML and DM has the ability to analyze raw/multidimensional data of brain abnormalities, microbial toxicity, microbiome chages

and COVID-19 patient lab information that is available at medical or clinical databases or hospitals. After targeted classification, these information and data could present regular patterns involved in brain disease development. Yielded computing data is useful ti introduce and determine correlations between different characteristics such as patients' personal data, disease symptoms or even diseae predictions. One of the most crucial aspects of ML in the case of data analysis is helping physicians in more accurate diagnosis of diseases and choosing the appropriate treatment for patients with significant changes in their microbiome golden ratio or microbial toxins profiles that can lead to neuronal dysfunctions[31]. Today, the use of technology and science of machine learning in the prevention, early diagnosis and treatment of many Alzheimer's, dementia, and Parkinson's disease are all on the rise [32]. Better early prognosis improves the qualification of preventing or theurapetic decisions for physicians, minimizing different medical errors, and could decline the cost and time of diagnosis, or indeed rescues and fullfill patients [33]. Natural language, Network Diffusion algorithm, Image processing and volumetric information, Time-series data, Graph data, support vector machine, and General data and multimodal data are some of the different types of ML data categories and methos that are now used to select the best ML model for a given problem based on different neurodegenerative diseases [32]. Scientists use 2D, 3D, graph convolutional neural network models, specialized natural language processing tools (BERT, SpaCy, CoreNLP, SyntaxNet, etc.), Hierarchical Basin models (SVMs, for example), random forests, and variations-as many ML models Use an autoencoder to diagnose Alzheimer's disease (AD), Parkinson's disease (PD), or to assess dementia categorization. We also used a cutting-edge machine learning (ML) model to predict the development of molecular fingerprints in amyotrophic lateral sclerosis (ALS) and the side effects of various medicines [32, 34].

Different neurodegenerative disease-related data types (Neuroimaging, cognitive performance tests, transcriptomic data, biomarker data, motor performance test and metabolomics data) now conventionally used by machine learning algorithms for disease progression evaluation [32, 35].

ML has also been found to be beneficial in identifying microbial and microbial toxin-related diseases, including as septicemia, nosocomial infections, surgical site infections (SSIs), and other postoperative infections, as well as evaluating and forecasting microbial test findings. Increase site-specific infections such as general infections, musculoskeletal infections, antibiotic prescriptions, deep fungal infections, and urinary tract infections (UTI) are monitored and tracked [27].

Machine learning can be used in many areas because of the infectious nature of Covid-19 and the effect that microbial profiles and microbial toxins can have on a patient's brain-neural network. Medical imaging, drug discovery, vaccine development, molecular biology and neuro-infection control are all commonalities between neuropsychiatric and infectious diseases that can be practiced under the supervision of machine learning monitoring [36].

4. Comprehensive conclusion

With the emergence of the COVID19 pandemic, human populations today are experiencing unprecedented health protocols. Some of these precautions have become commonplace. Like the constant use of hand sanitizers and new eating habits. These procedures can affect the amount and type of microbiota and microbial noxins volume in the body. For example, it is expected that as a result of overusing of hand sanitizers and antibiotics, the golden ratio of the human microbiome changes, so does the total available LPS of the body. The presence of such microbial toxins, which are themselves the cause of neural degeneration and one of the most prevalence natural leaders of neurodegenerative diseases in the body, is a very important caution alarm. Because LPS is not the only microbial toxin that is expected to increase in the body during the Covid-19 pandemic. Undoubtedly, such changes are being experienced chronically every day in human populations, and their effects on the body's defense systems and the growth of brain NN will be seen in humans. Our hypothesis is that the use of various information related to neuropsychiatric problems in neurodegenerative diseases and its association with microbial profiles and microbial toxins in COVID-19 patients will be a new promising and highly advanced approach in the diagnosis and treatment of the disease in the future. By monitoring and analyzing microbial toxin and considering neurological disease data via ML models, a new approach may be taken to reduce the potential

of neurodegeneration in human body during the COVID-19 pandemic.

Authors' contributions

AS: Collecting and summarizing Neurology-related articles. MD: Collecting and summarizing Neurology-related articles. MGH: Collecting and summarizing Both Neurology and Machine learning-related articles. SB: Collecting and summarizing Both Neurology and Microbial toxins-related articles. EGH: EndNote library preparation and referencing manuscript body. AB: Collecting and summarizing microbiome-related articles. AK: Collecting and summarizing microbiome-related articles. AR: Journal finding and edit files based on reviewers comments. MH: Suggesting the idea of article, writing first draft of article, scientific editing. All authors read and approved the final version of paper.

Conflict of interests

None to declare.

Ethical declarations

This review article has no Ethical declarations.

Financial support

Financial support of this review article has based on personal foundation.

References

1. Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaieski DF, Yaffee AQ, et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. J Glob Infect Dis. 2020; 12(2):47-93.
2. Malik YS, Kumar N, Sircar S, Kaushik R, Bhat S, Dhama K, et al. Coronavirus Disease Pandemic (COVID-19): Challenges and a Global Perspective. Pathogens. 2020; 9(7):519.
3. Woods JA, Hutchinson NT, Powers SK, Roberts WO, Gomez-Cabrera MC, Radak Z, et al. The COVID-19 pandemic and physical activity. Sports Med Health Sci. 2020; 2(2):55-64.
4. Khanizadeh A-M, Ejlali M, Karimzadeh F. The Effect of SARS-COV-2 Viruses on the Function of Different Organs, Especially the Nervous System. Neurosci J Shefaye Khatam. 2020; 8(3):111-21.
5. Sheppard O, Coleman MP, Durrant CS. Lipopolysaccharide-induced neuroinflammation induces presynaptic disruption through a direct action on brain tissue involving microglia-derived interleukin 1 beta. J Neuroinflammation. 2019; 16(1):106.
6. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. Cell. 2020; 183(1):16-27.e1.
7. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020; 87:18-22.
8. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses. 2019; 12(1):14.
9. Herrera-Rincon C, Paré JF, Martyniuk CJ, Jannetty SK, Harrison C, Fischer A, et al. An in vivo brain-bacteria interface: the developing brain as a key regulator of innate immunity. NPJ Regen Med. 2020; 5:2.
10. Babakhani S, Hosseini F. Gut Microbiota: An Effective Factor in the Human Brain and Behavior. Neurosci J Shefaye Khatam. 2019; 7(1):106-18.
11. Johnson KV. Gut microbiome composition and diversity are related to human personality traits. Hum Microb J. 2020; 15.
12. Mohajeri MH, La Fata G, Steinert RE, Weber P. Relationship between the gut microbiome and brain function. Nutr Rev. 2018; 76(7):481-96.
13. Smith LK, Wissel EF. Microbes and the Mind: How Bacteria Shape Affect, Neurological Processes, Cognition, Social Relationships, Development, and Pathology. Perspect Psychol Sci. 2019; 14(3):397-418.
14. Ghasemi-Varnamkhasti M, Mohtasebi SS, Siadat M, Balasubramanian S. Meat quality assessment by electronic nose (machine olfaction technology). Sensors (Basel). 2009; 9(8):6058-83.
15. Tseng C-Y. Effects of Atypical Neurotoxins on the Developing Fetal Brain. Medical Toxicology: IntechOpen; 2019.
16. Child NSCotD. Early exposure to toxic substances damages brain architecture: Harvard University, Center on the Developing Child; 2006.
17. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation. 2019; 16(1):53.
18. Smythies LE, Smythies JR. Microbiota, the immune system, black moods and the brain-melancholia updated. Front Hum Neurosci. 2014; 8:720.
19. Whitton PS. Inflammation as a causative factor in the aetiology of Parkinson's disease. Br J Pharmacol. 2007; 150(8):963-76.
20. Martins NRB, Angelica A, Chakravarthy K, Svidinenko Y, Boehm FJ, Opris I, et al. Human Brain/Cloud Interface. Front Neurosci. 2019; 13:112.
21. Morris G, Fernandes BS, Puri BK, Walker AJ, Carvalho AF, Berk M. Leaky brain in neurological and psychiatric disorders: Drivers and consequences. Aust N Z J Psychiatry. 2018; 52(10):924-48.
22. Maguire M, Maguire G. Gut dysbiosis, leaky gut, and intestinal epithelial proliferation in neurological disorders: towards the development of a new therapeutic using amino acids, prebiotics, probiotics, and postbiotics. Rev Neurosci. 2019; 30(2):179-201.
23. Tantillo E, Colistra A, Vannini E, Cerri C, Pancrazi L, Baroncelli L, et al. Bacterial Toxins and Targeted Brain Therapy: New Insights from Cytotoxic Necrotizing Factor 1 (CNF1). Int J Mol Sci. 2018; 19(6):1632.
24. Popoff MR, Poulain B. Bacterial toxins and the nervous system: neurotoxins and multipotential toxins interacting with neuronal cells. Toxins (Basel). 2010; 2(4):683-737.

25. Farthing MJ. Enterotoxins and the enteric nervous system--a fatal attraction. Int J Med Microbiol. 2000; 290(4-5):491-6.
26. Kouanda B, Sattar Z, Geraghty P. Periodontal Diseases: Major Exacerbators of Pulmonary Diseases? Pulm Med. 2021; 2021:4712406.
27. Luz CF, Vollmer M, Decruyenaere J, Nijsten MW, Glasner C, Sinha B. Machine learning in infection management using routine electronic health records: tools, techniques, and reporting of future technologies. Clin Microbiol Infect. 2020; 26(10):1291-9.
28. Alzubi J, Nayyar A, Kumar A, editors. Machine learning from theory to algorithms: an overview. J Phys Conf Ser; 2018: IOP Publishing.
29. Patel L, Shukla T, Huang X, Ussery DW, Wang S. Machine Learning Methods in Drug Discovery. Molecules. 2020; 25(22):5277.
30. Strieth-Kalthoff F, Sandfort F, Segler MHS, Glorius F. Machine learning the ropes: principles, applications and directions in synthetic chemistry. Chem Soc Rev. 2020; 49(17):6154-68.
31. Mahon CR, Lehman DC, Manuselis G. Textbook of diagnostic microbiology-e-book: Elsevier Health Sciences; 2018.
32. Myszczynska MA, Ojamies PN, Lacoste AMB, Neil D, Saffari A, Mead R, et al. Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. Nat Rev Neurol. 2020; 16(8):440-56.
33. Christakis NA. Death foretold: prophecy and prognosis in medical care: University of Chicago Press; 2001.
34. Ji S, Yang M, Yu K. 3D convolutional neural networks for human action recognition. IEEE Trans Pattern Anal Mach Intell. 2013; 35(1):221-31.
35. ten Bosch L, Ernestus M, Boves L. Analyzing Reaction Time Sequences from Human Participants in Auditory Experiments Proceedings of Interspeech 2018: The 19th Annual Conference of the International Speech Communication Association, pages 971-9752018.
36. Peiffer-Smadja N, Rawson TM, Ahmad R, Buchard A, Georgiou P, Lescure FX, et al. Machine learning for clinical decision support in infectious diseases: a narrative review of current applications. Clin Microbiol Infect. 2020; 26(5):584-95.